Successful *in vitro* fertilization pregnancy (IVF) after conservative management of endometrial cancer

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ABSTRACT

Objective: To report a successful IVF pregnancy in a couple after conservative treatment of endometrial cancer. **Design**: Case report and literature review. **Setting**: ASL città di Torino – SC PMA, Valdese dpt. **Patient(s)**: A 32-year-old white woman. **Main Outcome Measure(s)**: Successful pregnancy after conservative management of endometrial cancer. **Intervention(s)**: Grade 1 endometrial adenocarcinoma diagnosed at hysteroscopy, followed by dilatation and curettage (D&C). On follow-up D&C, pathologic examination was normal after high-dose progesterone therapy. The patient subsequently underwent an IVF cycle with transfer of one embryo. **Result(s)**: The patient delivered a baby boy with a vaginal delivery at 37 weeks of gestational age. She is currently undergoing follow-up, and hysterectomy and bilateral salpingo-oophorectomy have not yet been performed. **Conclusion(s)**: In carefully chosen situations, deferring surgery in infertile patients with endometrial cancer may be a viable option permitting subsequent successful pregnancy.

KEYWORDS

IVF, endometrial cancer, save fertility, pregnancy conservative management.

Introduction

Endometrial cancer (EC) ranks among the most prevalent gynecological malignancies globally [1,2], mainly affecting postmenopausal women. However, a notable proportion of EC cases, approximately 7.1%, occur in women aged 20 to 44 years, and strikingly, over 70% of these women are nulliparous at the time of diagnosis [3,4]. The characteristic presentation often includes vaginal bleeding [5,6], enabling early detection and intervention, contributing to a favorable five-year survival rate exceeding 95%.

EC has been categorized into two primary types, Type I and Type II, each with distinct clinical and pathological features.

Type I EC is predominantly characterized by genetic mutations, notably microsatellite instability, and is often linked to lifestyle factors such as obesity, hormonal imbalances (like those seen in polycystic ovarian syndrome), and a hyperestrogenic state [7]. The latter associated with a high body mass index (BMI) is, in part, explained by the peripheral conversion of androgens to estrogen in adipose tissue via aromatase.

Type II ECs, on the other hand, are typically associated with older age at diagnosis, advanced disease stage at presentation, higher tumor grade, and non-endometrioid histopathological subtypes, including serous, clear-cell, and undifferentiated carcinomas. These cancers tend to have a relatively poor prognosis [8].

Understanding the risk factors associated with EC is essential for both prevention and management. Key risk factors include:

- high BMI: excess body weight is a significant contributor to the hyperestrogenic state, increasing EC risk;
- hyperestrogenic states: beyond BMI, conditions such as nulliparity, estrogen-releasing tumors, early menarche, late menopause, and exposure to unopposed estrogen further elevate the risk of EC.
- systemic diseases: conditions like hypertension and diabetes mellitus are linked to an increased risk of EC [4,9,10].

The incidence of EC among women of reproductive age is on the rise, necessitating fertility-sparing management strategies. Preserving fertility while effectively treating EC is a delicate balance, requiring careful consideration [11].

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Fertility-sparing approaches

Various fertility-sparing approaches have been explored for young women with EC who wish to preserve their reproductive potential.

Hormonal therapies. These therapies aim to induce regression or stabilization of the tumor. Progestin-based treatments, such as medroxyprogesterone acetate and megestrol acetate, are commonly employed and have shown success in achieving

complete or partial response in many cases [4,12,13].

In addition to oral therapy, another viable option for administering progesterone treatment is through the use of a temporary levonorgestrel-releasing intrauterine device (LNG-IUD). This approach is particularly beneficial when seeking to avoid the systemic adverse effects associated with high-dose oral progestins. One significant advantage is the localized nature of the therapy. By delivering the progestin directly to the uterine lining, the LNG-IUD minimizes systemic absorption. This, in turn, reduces the risk of the systemic side effects commonly associated with high-dose oral progestins.

These side effects, which can include mood swings, weight gain, and changes in appetite, are less likely to occur with the LNG-IUD due to its localized action. Moreover, the LNG-IUD provides the convenience of long-term treatment without the need for daily medication. It can typically remain in place for several years, ensuring a sustained and consistent release of hormone.

The choice between oral progestin therapy and LNG-IUDs, as well as other treatment options, should be based on careful consideration of the patient's specific medical condition, preferences, and individual clinical factors. The suitability of LNG-IUDs for fertility preservation in patients with EC will depend on various factors, including the patient's overall health and the stage and characteristics of the cancer. Therefore, it is crucial for patients to engage in thorough discussions with their healthcare providers to determine the most appropriate and effective treatment strategy tailored to their unique circumstances and goals [14,15].

Hysteroscopic resection. In select cases, hysteroscopic resection can be considered to remove small tumors or polyps while preserving the uterus [3].

Combination therapies. Some approaches combine progestin-based therapies including LNG-IUD with hysteroscopic resection for improved outcomes [14].

Patient selection criteria

Selecting suitable candidates for fertility-sparing management is paramount. Factors that guide patient selection include:

- age: a younger age at diagnosis is generally more favorable for fertility preservation;
- cancer stage: early-stage EC (Stage I) is more amenable to fertility-sparing approaches;
- histological type: patients with endometrioid-type EC may be better candidates than those with non-endometrioid histologies;
- fertility desires: the patient's preferences with regard to future childbearing play a crucial role in decision-making [3,4].

Follow-up and surveillance

Post-treatment follow-up and surveillance are essential to assess treatment effectiveness and monitor for any disease recurrence. Regular imaging, biopsies, and clinical assessments are standard components of follow-up care.

Challenges and limitations

Managing EC in young women seeking fertility preservation is challenging for several reasons. These include the rarity of EC in this demographic, the need for individualized treatment plans, and the limited long-term data on the outcomes of fertility-sparing approaches.

Future directions

Ongoing research aims to refine and expand fertility-sparing options, improve patient selection criteria, and enhance our understanding of the long-term outcomes and safety of these approaches. Novel treatments and tailored management strategies are areas of active investigation.

Women younger than 40 years of age tend to have well-differentiated tumors and early-stage disease. Women of reproductive age who wish to preserve their fertility may not want to undergo definitive surgical treatment. We describe the case of a patient who had a successful IVF cycle resulting in a pregnancy after conservative treatment of endometrial cancer.

Case report

In September 2020, a 32-year-old non-obese (BMI 20.6), white, nulligravid woman presented at our institution with a diagnosis of endometrial intraepithelial neoplasia. This had been diagnosed incidentally during an ultrasound examination, which revealed a heterogeneous endometrium. Her medical, surgical, and social history was unremarkable. She had a unicornuate unicollis uterus with a suspected accessory right cornus. She had no family history of diabetes, hypertension, or cancer, and she did not smoke. The patient declined standard surgical management and requested conservative treatment in an attempt to preserve her fertility. A gynecologic oncologist evaluated the patient and explained the risks of conservative management. Progestin therapy was recommended; the patient was prescribed oral megestrol acetate (medroxyprogesterone acetate, Farlutal®, 20 mg) once daily, and an LNG-IUD (Mirena® Bayer Health Care Pharmaceutical Inc, Wayne, NY, USA) was inserted. The IUD was removed when the patient was ready to attempt pregnancy.

Follow-up: Subsequent hysteroscopies showed pseudodecidualization of the endometrium, consistent with exogenous hormone therapy, but no evidence of residual adenocarcinoma. It was decided to use IVF treatment to optimize the patient's potential for fertility, and attempt to achieve a viable pregnancy without further delay. Hysterectomy was recommended following fertility treatment.

The patient underwent her first IVF cycle in November 2021. Nine oocytes were obtained (6 in metaphase II, 2 in metaphase I, and one germinal vesicle), three of which were fertilized. Two embryos and one blastocyst were obtained. On February 8, 2022, after removing Mirena® in December 2021, one blastocyst was transferred, resulting in a pregnancy. Unfortunately, in March, at 8 weeks and 5 days of gestational age,

a miscarriage was diagnosed. Hysteroscopy after the miscarriage, performed in May, showed the absence of malignant neoplasm, so the patient underwent her second transfer. On June 6, 2022, one grade-A day-3 embryo was transferred, but no pregnancy resulted. On August 2, 2022, the last embryo (also grade-A, day-3) was transferred and this resulted in a full-term pregnancy. The patient successfully delivered a healthy baby boy at 37 weeks and 2 days of gestational age, after experiencing premature rupture of the membranes. The patient had a normal postpartum course, was breastfeeding, and took a progestin-only pill for contraception. It is reassuring to learn that the patient has undergone two hysteroscopies that did not reveal any neoplasms. The patient's healthcare team will continue to assess her condition and determine the most appropriate course of action based on her individual circumstances.

IVF cycle protocol: As mentioned, the IVF cycle was initiated in November 2021; nine eggs were retrieved, three of which were fertilized. The patient's peak estradiol level on the day of hCG administration was 670.4 pg/mL. She had an initial hCG level of 1283.2 mIU/mL 13 days after the last embryo transfer (ET). 21 days after ET, she had an hCG level of 2235.9 mIU/mL, and an ultrasound examination confirmed the pregnancy. The patient had a normal postoperative course, was breastfeeding, and took a progestin-only pill for contraception

IVF cycle protocol: The stimulation cycle was performed using alpha follitropin (Ovaleap®, 300 IU/d) in addition to the patient's therapy as prescribed by her oncologist (Mirena® and Farlutal®). Human chorionic gonadotropin (Gonasi®), 10,000 U, was administered when at least two follicles with a mean diameter of 18 to 20 mm were present, and the estradiol level was greater than 500 pg/mL. Transvaginal retrieval of oocytes was performed 36 hours after hCG administration. ET was done on the patient's natural cycle triggered by HCG 5000 UI prior to measurement of P4. After the transfer, the patient continued taking levothyroxine 25 mcg (prescribed during preconceptional medical check-ups), folic acid 400 mcg (1 tablet daily), and started progesterone 400 mg (2 vaginal suppositories daily), cardioASA100 mg (1 tablet daily), and methylprednisolone 4 mg (1 tablet daily).

Conclusions

Fertility-preserving treatment can be a viable option for younger patients diagnosed with stage IA EC who express a desire to become pregnant. However, it is important to acknowledge that while this approach holds promise, the available evidence to support its efficacy remains somewhat limited.

The first step in pursuing fertility preservation in EC patients is to conduct a thorough evaluation and ensure an accurate diagnosis. Not all patients are suitable candidates for this approach, so individualized assessments are essential to determine eligibility.

Several treatment options exist for fertility preservation in EC, and they can be tailored to the patient's specific circumstances. These options include oral progestin therapy, the use of LNG-IUDs, hormone replacement therapy (HR), gonadotropin-releasing hormone agonist therapy, and the use of aromatase inhibitors, either alone or in combination with other treatments.

Combination therapy involving HR following medical treatment may offer an improved response rate. Nevertheless, further research is required to establish the most effective dosage, route of administration, and treatment duration for these combination approaches.

Once a complete response is achieved, it is advisable for women wishing to conceive to attempt pregnancy as promptly as possible. Assisted reproductive technologies may be considered, in order to expedite the conception process compared with spontaneous conception.

Regular follow-up with oncology specialists, typically scheduled at six-monthly intervals, is an integral part of the treatment plan. This ongoing monitoring is essential to track the patient's progress and evaluate the response to treatment.

Crucially, the treatment approach must be personalized to accommodate the individual patient's characteristics, such as age, BMI, tumor grade, and response to treatment. Recognizing and addressing these unique factors is essential to optimize outcomes and enhance the chances of successful fertility preservation in EC patients.

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